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METHODS FOR REDUCING OR ELIMINATING POST-SURGICAL ADHESION FORMATION

5   The present invention relates to the discovery that the use of biodegradable

polymeric compositions can prevent or reduce communication between two sites after surgery

and thereby significantly reduce and in some cases, actually prevent post-operative adhesions

which often occur during the initial phases of post-surgical repair.

10   Background of the Invention

        A major clinical problem relating to surgical repair or inflammatory disease is

adhesion which occurs during the initial phases of the healing process after surgery or disease.

Adhesion is a condition which involves the formation of abnormal tissue linkages. These

15   linkages which form can impair bodily function, produce infertility, obstruct the intestines and

other portions of the gastrointestinal tract (bowel obstruction) and produce general

discomfort, e.g. pelvic pain. The condition can be life threatening. The most common form of

adhesion occurs after surgery as a result of trauma, although adhesion may occur as a result of

other processes or events such as pelvic inflammatory disease, mechanical injury, radiation

20   treatment and the presence of foreign material.

        Various attempts have been made to prevent postoperative adhesions. For

example, the use of peritoneal lavage, heparinized solutions, procoagulants, modification of

surgical techniques such as the use of microscopic or laparoscopic surgical techniques, the

elimination of talc from surgical gloves, the use of smaller sutures and the use of physical

barriers (films, gels or solutions) aiming to minimize apposition of serosal surfaces, have all

been attempted. Unfortunately, very limited success has been seen with these methods.

Barrier materials, in various forms such as films and viscous intraperitoneal solutions, which

5   are designed to limit tissue apposition, have also met with only limited success. The best of

these barrier materials include cellulosic barriers, polytetrafluoroethylene materials, and

dextran solutions. Also, a number of films based on polylactic acid, polyglycolic acid and

copolymers of the two have proven to be unsuccessful. Indeed, most barrier materials have

met with failure because these materials can induce untoward biological effects, e.g., foreign

10   body reaction.

ckd   United States patent number 5,410,016 to Hubbell, et al. is directed to

photopolymerizable biodegradable gels for use as adhesion barriers, as control release systems

for drugs, to provide temporary protection of tissue surfaces and for adhering or sealing

15   tissues together. Hubbell, et al. discloses water-soluble macromonomers containing

photopolymerizable groups on each end which are administered or placed on tissues prior to a

photopolymerization step. After administration, the macromonomers are photopolymerized in

situ in order to produce a crosslinked polymer on the tissue. The method of Hubbell, et al.

suffers from the disadvantage that it produces non-uniform, highly crosslinked, weak

20   polymers. Furthermore, the Hubbell system is a cumbersome system, requiring additional

equipment and expertise which adds to the cost of the treatment. In addition, the method

suffers from the disadvantage that the patient must be irradiated with energy to polymerize the

macromonomers during or after surgery, potentially compromising sterility and complicating

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and prolonging the surgical process. In contrast to the polymers of Hubbell, et al., the present polymers and methods make use of substantially non-water soluble triblocks and which are non-crosslinked and prepared prior to introduction into the patient.

5   Ideally, a physical barrier for adhesion prevention should be completely absorbable and nonreactive. In addition, it should stay in place in the body with a minimum of suturing or stapling.

Objects of the Invention

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It is an object of the present invention to provide polymeric barriers which may be used to substantially prevent tissue to tissue adhesions and adhesions between tissue and implants and devices.

15   It is an additional object of the invention to provide polymeric materials in film, other solid structures such as rods, cylinders, porous structures such as foams, dispersions, viscous solutions, liquid polymers, sprays or gels which may be administered easily and with uniform results after surgery.

20   It is a further object of the invention to provide polymeric materials which may be used to substantially prevent adhesions and which may be effective for delivering bioactive agents.

It is yet an additional object of the invention to provide bioabsorbable polymeric materials which can be produced in a variety of formulations which have acceptable strength, are non-reactive with patient tissue and are bioabsorbable.

5   It is yet another object of the present invention to provide polymeric barriers which can be used in various forms, e.g., films, other structures such as rods and cylinders, foams, gels, dispersions, liquid polymers, sprays or viscous solutions, to provide flexibility in administration and use.

10   These and/or other objects of the invention may be readily gleaned from the detailed description of the present invention which follows.

Summary of the Invention

15   The present invention relates to a method for eliminating or reducing post-surgical tissue adhesions using polymeric materials which are non-crosslinked, substantially integral and relatively rapidly bioabsorbable. It is the combination of these characteristics in polymers of the present invention which has produced favorable results in substantially reducing or even eliminating post-operative adhesions. Moreover, the method of

20   the present invention is performed simply and in a cost-effective manner without the need for additional or expensive equipment. Unlike the prior art methods, the present invention is used under sterile conditions without exceptional efforts to maintain sterility and avoids the necessity of irradiating the patient. In addition, certain polymers used in the present invention

(e.g. films or related preformed structures of polymer) exhibit sufficient strength and flexibility to be able to conform to a site to be protected and allow a suture to hold a polymer structure in place at the site of surgery.

5   It now has been discovered that the substantially non-crosslinked polymers according to the present invention, which are able to generate an integral barrier, are advantageously employed in reducing and even completely eliminating post-surgical adhesions. The present method comprises administering or affixing to an area in a patient's body at risk for developing adhesions, a polymeric composition comprising chain-extended

10   poly(hydroxycarboxylic acid)/poly(oxyalkylene) ABA triblocks. In many embodiments, the method comprises administering the instant polymer compositions to a site within the patient's body which has been subjected to surgical repair or excision. In the present invention, the polymeric material provides a barrier to prevent adhesions from forming. After this period of protection, the polymer will degrade and will be resorbed within the patient's body and/or

15   excreted from the patient's body. According to the present method, problems associated with non-absorbtion or foreign body reactions are significantly reduced or prevented.

        The polymer may be administered in various forms such as films, other structures including rods, cylinders, foams, dispersions, viscous solutions, liquid polymers,

20   sprays or gels. The form a polymer takes at the surgical site will depend upon the type of surgery which has been performed or the condition which is to be treated and the site to be treated. In addition, the need to deliver the polymer to a particular site within the body may be determinitive of the form in which the polymer is delivered. The present method may be

used after virtually any surgery to prevent tissue adhesion which occurs during the initial

phases of post-surgical repair. Thus, in all applications where tissue is being repaired or

excised, the polymers according to the present invention find utility to prevent adhesions.

Generally, the polymers are used to prevent tissue to tissue adhesion and adhesions beween

5   tissues and implants or devices, which occur after surgical procedures, as well as other

conditions, including certain disease states.

       The present polymers are based on poly (hydroxy-carboxylic

acid)/poly(oxyalkylene) ABA triblocks, where A is a polymeric unit preferably derived from an

10   aliphatic α-hydroxy carboxylic acid or related ester, such as, for example, lactic acid, lactide,

glycolic acid, glycolide, or a related aliphatic hydroxycarboxylic acid or ester (lactone) such as,

for example, ϵ-caprolactone, δ-glutarolactone, δ-valerolactone, γ-butyrolactone and mixtures,

thereof. The use of α-hydroxyacids in the present invention is preferred. The A block of the

triblocks used in the present invention preferably comprises a poly(α-hydroxy-carboxylic acid),

15   for example, poly(glycolic acid), poly(L-lactic acid) and poly(D,L-lactic acid), because these

polymers will degrade and produce monomeric units which may be readily metabolized by the

patient. The B block in the triblocks used in the present invention are generally hydroxyl or

amine terminated poly(oxyalkylene) blocks and are preferably either poly(ethylene oxide)

homopolymers or poly(ethylene oxide)-co-poly(propylene oxide) block copolymers.

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       The above triblocks are preferably end-capped with hydroxyl groups and are

chain-extended using difunctional chain extenders such as diisocyanates, dicarboxylates,

diesters or diacyl halide groups in order to chain extend the triblocks into high molecular

weight polymer chains. Alternatively, the triblocks may be end-capped with groups such as carboxylic acid moieties or ester groups (which may be reacted directly as ester groups, activated as "active" ester groups or converted to active acyl groups such as acyl halides) or isocyanate groups and then reacted with difunctional chain extenders such as diols, diamines,

5   hydroxylamines, or polyoxyethylene (polyethylene glycol) chain extenders (especially, in the case of water soluble or water dispersible gels, dispersions or viscous solutions) among others, to produce chain extended polymers having high molecular weight. It is the fact that the polymers according to the present invention comprise chain-extended trimers which have relatively high molecular weights and are substantially non-crosslinked, which provides

10   polymeric characteristics which are advantageously employed in barriers of various forms including a preformed structure such as a film, rod, tube, bead, foam or ring or dispersions, sprays, gels, liquid polymers, viscous liquids and viscous solutions, among others, according to the present invention.

15   Preferred polymers for use in the present invention have the following characteristics: they are chain-extended, substantially non-crosslinked and biodegradable. Preferred polymers are also non-reactive, i.e., they do not produce an unintended or adverse tissue reaction. The present polymers are advantageously used as barrier materials to reduce or prevent adhesion. Polymers used in various preformed structures such as films according to

20   the present invention are sufficiently flexible to enable the polymer to substantially conform to the surface of the tissue to be treated, yet at the same time have sufficient strength to function as an integral and therefore, effective barrier to allow suturing the material to tissue. Polymers used in other forms such as gels, dispersions and viscous solutions according to the present

invention also have sufficient structural integrity to be delivered to a site within the body and prevent adhesions at the same time that the polymers are water soluble and/or water dispersible in order to be delivered.

In the present invention, PELA is the generic name used to denote the preferred polymers comprising poly(ethylene oxide) and poly(lactic acid) blocks, being chain extended with a diisocyanate, most preferably hexamethylene diisocyanate. PELA polymers are generally designated with respect to their composition by the average molecular weight of the poly(ethylene oxide) chain and by the (EO/LA) ratio of the ABA triblock, where EO is the number of ethylene oxide units present in the poly(ethylene oxide) B block and LA is the total number of lactoyl units present in two A blocks of the ABA triblock.

In the present invention, the ABA triblock is a substantially non-water soluble unit preferably comprising poly(α-hydroxy acid) blocks and ethylene glycol, diethylene glycol and poly(ethylene oxide) chains or poly(ethylene oxide)-co-poly(propylene oxide) block copolymers. The A block of the ABA triblocks of the present polymers is biodegradable and ranges in size from one monomeric unit (a monomeric unit within the A block being considered lactic acid, glycolic acid or a related hydroxy acid unit even where lactide and/or glycolide or related reactants containing more than one hydroxyacid unit are used to produce the A block) up to about 200 or more monomeric units, with a preferred size ranging from about 4 to about 50 units, more preferably about 6 to about 30 units, even more preferably about 8 to about 16 monomeric units, which length depends upon the length or molecular

weight of the B block combined with the A block in triblocks according to the present invention. It is to be noted that the size of the A block may well fall outside of the above range, depending upon the overall physical characteristics of the ABA triblock formed and the size of the B block.

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The A block is derived preferably from an α-hydroxy acid as described above, more preferably from units of glycolic acid, lactic acid (preferably L or D,L mixtures to promote bioabsorbability) or mixtures thereof, in the form of glycolide or lactide reactants (as explained in greater detail hereinbelow). In the final polymers to be used to reduce or prevent

10 post-operative adhesion, the A blocks tend to create hard domains in the matrix and generally provide strength and structural integrity to the polymer. The A block is non-water soluble and is sized in combination with the more water soluble/water dispersible B block in order to promote phase separation between the the A and B blocks in the ABA triblock and the final polymer to be used to prevent or reduce adhesions. Thus, the A block instills the final

15 polymer with essential structural characteristics, which, in combination with the B block, results in a polymer which has excellent anti-adhesion characteristics (believed to be instilled by the B block) in combination with strength, structural integrity and biodegradability instilled by the A block. In addition, the length of the A block is important for providing a material with a phase separated microstructure.

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The B block preferably comprises poly(ethylene oxide) or poly(ethylene oxide)-co-poly(propylene oxide) block copolymers and other PEO-rich chains which fall in the molecular weight (M_w) range as defined hereinbelow. The B block may preferably vary in size

from about 160 Da (dalton units) up to about 200,000 Da or higher, with a more preferred range of about 1,000 Da up to about 20,000 Da. Even more preferably, the B block is a poly(ethylene oxide) ranging in size from about 3,000 to about 10,000 Da. Based upon the teachings of the present invention, one of ordinary skill will now know to vary the length of the B block and the A block to provide polymers having excellent anti-adhesion properties.

The triblocks according to the present invention are generally described according to the length (number of monomeric repeating units) of the B block [preferably, poly(ethylene oxide), the repeating unit being in this case ethylene oxide units] divided by the total number of α-hydroxy acid units in both A blocks (preferably, lactic acid) of the ABA triblock. This ratio is referred to as the EO/LA ratio. Polymers comprised of ABA triblocks which are chain extended pursuant to the present invention also may be described in terms of an EO/LA ratio for this preferred polymer. These polymers may also be designated with respect to their composition by the average molecular weight of the poly(ethylene oxide) (PEG) chain and by the weight percentage of the PEG chain in the triblock. It should be noted, however, that in instances where the chain extender comprises a poly(ethylene oxide) chain, the EO/LA ratio for the chain extended polymer may vary considerably from the EO/LA ratio found in the ABA triblock (the total amount of EO may become considerably larger because of contribution of EO from the chain extender, and consequently, the EO/LA ratio for the polymer may be considerably larger than it is for the ABA triblock). Likewise, the weight percentage of PEG found in such a polymer may also be quite different from that found in the ABA triblock.

The concept of the EO/LA ratio may be exemplified by a polymer described as a poly(ethylene oxide)-lactic acid block copolymer (PELA) 6,000/3.8, which is a hexamethylene diisocyanate chain extended ABA triblock copolymer comprising PEG chains having an average molecular weight of 6,000 and an EO/LA ratio of 3.8. The triblock in this

5   polymer comprises, therefore, a 6,000 molecular weight PEG segment for the B block containing approximately 136 ethylene oxide units and two A blocks each containing, on average, approximately 18 LA units. Alternatively, the same polymer can be designated as 6,000/69.8%, where 6,000 is the average molecular weight of the PEG chains, and 69.8% is the weight percentage of PEG in the ABA triblock. For this PELA 6,000/3.8 polymer, the

10   molecular weight of the triblock is approximately 8592 (6,000 for the PEG chain and two poly (lactic acid) A blocks each having a molecular weight of approximately 1296, for a total for the two A blocks of 2592). The weight percentage of the PEG block in this triblock is, accordingly, 69.8% (6,000/8592).

15   The EO/LA ratio for polymers according to the present invention preferably ranges from about 0.5 to about 5.0, more preferably about 2.0 to about 4.5, even more preferably about 2.5 to about 3.5 and most preferably about 3.0. In certain instances, the EO/LA ratio may fall outside of these ranges, depending upon the final characteristics of the polymers which are desired. Preferred EO/LA ratios for individual polymers may also vary

20   according to the size of the B block and the type of chain-extender which is used. Generally, as the size (molecular weight) of the B block in the triblocks increases, the preferred EO/LA ratio will tend to be somewhat less than in triblocks and polymers where the size of the B block is less.

Tailoring the properties of the antiadhesion barriers generated by the present polymers is based upon combining (a) the enhanced antiadhesion properties attributed, by way of theory, by the PEG (B block) segments; (b) the biodegradability of the poly(α-hydroxy acid) A blocks; and (c) the mechanical properties derived from the partially phase separated microstructure of the polymeric matrix.

The higher the PEG (B block) content, the less efficacious the polymer will be as an antiadhesion barrier, but also the faster the polymer degrades. Since there is a requirement for the barrier to stay in place separating the relevant tissues for a determined period of time, there is an optimal EO/LA ratio which combines maximum PEG content with the biologically required residence time. In agreement with these basic considerations, preliminary animal data indicate that polymers of the present invention comprising PEG chains of a 6,000 molecular weight and having an EO/LA ratio of approximately 3.0, display optimal properties as antiadhesion barriers.

Based upon the teachings of the present invention, one of ordinary skill in the art will now know to vary the length of the A block to the B block in a manner which provides polymers having excellent structural integrity, biodegradability and activity which substantially inhibits post-operative adhesion.

The polymers according to the present invention are chain-extended and attain high molecular weight. They are substantially non-crosslinked. In order to increase the

molecular weight of the polymer produced, the hydroxyl end-capped ABA triblock is chain-extended using difunctional compounds such as diisocyanate, dicarboxylic acid compounds or derivatives of dicarboxylic acids such as diacyl halides. Preferably, the nucleophilic end-capped triblocks are chain-extended with diisocyanate compounds in order to produce chain-extended polymers according to the present invention. In the case of structures such as films, the chain extenders are used to provide greater molecular weight to the triblocks, thus enhancing structural integrity. In the case of gels, liquid polymers and/or viscous solutions, the chain extenders provide not only high molecular weight and structural integrity, but also a degree of water solubility/dispersibility consistent with the solubility and/or dispersibility of these polymers in water and the delivery of these polymers to a site within the patient's body. Thus, the chain extenders provide all of these benefits without shortening the A blocks, which would hamper their beneficial morphological and mechanical effect.

The final polymers according to the present invention may be non-water soluble or in certain liquid, viscous solution and/or gel applications may absorb significant quantities of water.

The present invention therefore relates to polymer compositions and to methods of substantially reducing or preventing tissue adhesions in patients comprising exposing damaged tissue in a patient to a polymeric composition of the present invention in various forms, such as films, viscous solutions or gel forms. Depending upon the type of tissue to be treated, the extent of injury which has occurred, the nature of the surgical procedure performed and the way the polymer is administered, the polymeric composition

according to the present invention may be used advantageously in different forms such as an integral film, a dispersion as well as a gel or a viscous solution. The present polymers may be used in conjunction with any type of surgical procedure, and in particular, intraabdominal, intraperitoneal or in pelvic surgery. More specifically, the present polymers may be used to

5   substantially reduce or prevent adhesions in conjunction with musculoskeletal surgery, abdominal surgery, gynecological surgery, ophthalmic, orthopedic, central nervous system, cardiovascular and intrauterine repair.

Detailed Description of the invention

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The following terms shall be used throughout the specification to describe the present invention.

The term "adhesion" is used to describe abnormal attachments between tissues

15   or organs or between tissues and implants (prosthetic devices) which form after an inflammatory stimulus, most commonly surgery, and in most instances produce considerable pain and discomfort. When adhesions affect normal tissue function, they are considered a complication of surgery. These tissue linkages often occur between two surfaces of tissue during the initial phases of post-operative repair or part of the healing process. Adhesions are

20   fibrous structures that connect tissues or organs which are not normally joined. Common post-operative adhesions to which the present invention is directed include, for example, intraperitoneal or intraabdominal adhesions and pelvic adhesions. The term adhesions is also used with reference to all types of surgery including, for example, musculoskeletal surgery,

abdominal surgery, gynecological surgery, ophthalmic, orthopedic, central nervous system, cardiovascular and intrauterine repair. Adhesions may produce bowel obstruction or intestinal loops following abdominal surgery, infertility following gynecological surgery as a result of adhesions forming between pelvic structures, restricted limb motion (tendon adhesions)

5 following musculoskeletal surgery, cardiovascular complications including impairing the normal movement of the heart following cardiac surgery, an increase in intracranial bleeding, infection and cerebrospinal fluid leakage and pain following many surgeries, especially including spinal surgery which produces low back pain, leg pain and sphincter disturbance.

10 The terms "poly(ethlyene glycol)", "poly(oxyethylene)" and polyethylene oxide are used interchangably to describe the present invention.

The terms "poly(hydroxy carboxylic acid)" or "poly(α-hydroxy carboxylic acid)" are used to describe polyester A blocks of ABA triblocks used in polymeric

15 compositions according to the present invention where A is a polymeric polyester unit derived from an aliphatic hydroxy carboxylic acid or a related ester or dimeric ester and is preferably derived from an aliphatic α-hydroxy carboxylic acid or related ester, including a cyclic dimeric ester, such as, for example, lactic acid, lactide, glycolic acid, glycolide, or a related aliphatic hydroxycarboxylic acid or ester (lactone) such as, for example, ε-caprolactone, δ-

20 glutarolactone, δ-valerolactone, γ-butyrolactone and mixtures, thereof. The use of α-hydroxyacids and their corresponding cylic dimeric esters, especially lactide and glycolide in the present invention, is preferred.

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The term "non-water soluble" or "substantially non-water soluble" is used to describe ABA triblocks used in various forms such as films, gels, dispersions and viscous solutions according to the present invention. In the present invention, in forms such as viscous solutions, in which the polymers are substantially water soluble, the ABA triblocks are also non-water soluble. Non-water soluble triblocks are soluble in water up to a limit of no more than about 0.5-0.6 g per 100 ml of water, preferably less than about 0.2 g per 100 ml of water. In determining water solubility, triblocks according to the present invention are dissolved in, agitated or mixed in water at room temperature (i.e., at a temperature of about 20-23°C) for a period of two hours. It is noted that in the present invention, chain extended triblocks which are used to produce structures such as films according to the present invention are also substantially non-water soluble, i.e, they are limited in water solubility to no more than about 0.2 mg/ml. This limitation of water solubility reflects the fact that triblocks which are preferably used in the present invention comprise at least about 25-30% by weight of A blocks.

An amount of the two A blocks comprising at least about 25-30% by weight of the triblocks generally renders the ABA triblocks according to the present invention substantially non-water soluble. This characteristic is advantageous in the present polymeric compositions because the length and/or size of the A block instills structural integrity and biodegradability to the final polymer, but also, by virtue of the relative hydrophobicity of the block, tends to reduce the water solubility of the ABA triblock. Consequently, polymeric compositions according to the present invention which contain a proper balance of A blocks to B block have a slow rate of biodegradability and consequently, a longer period of interaction

with tissue to be protected from adhesion formation.

Polymers to be used in viscous solutions, dispersions and/or gels according to the present invention are preferably water soluble and/or water dispersible and use the same or

5 similar ABA triblocks used in polymeric structures such as films according to the present invention. In certain applications of the present inventions, in particular, in producing a liquid version which is substantially non-water soluble, having acceptable viscosity and flow characteristics for favorable administration, the polymers are actually substantially non-water soluble. Consequently, in applications such as films as well as in gel, dispersion and viscous

10 solution applications, regardless of the way the polymers are administered, the ABA triblocks which are preferably used are substantially non-water soluble.

The term "EO/LA ratio" is used to describe the relative amount of poly(ethylene oxide) or poly(ethylene oxide)-co-poly(propylene oxide) and hydroxy carboxylic

15 acid (preferably, α-hydroxy carboxylic acid, most preferably, lactic acid) which is used in ABA triblock copolymers and chain-extended polymers according to the present invention. This term refers to the length (number of monomeric ethylene oxide units) of the B block [preferably, poly(ethylene oxide)] divided by the total number of α hydroxy acid units in both A blocks (preferably, lactic acid) of the ABA triblock as described hereinabove. Polymers

20 comprised of ABA triblocks which are chain extended pursuant to the present invention are also described in terms of an EO/LA ratio. Preferred polymers according to the present invention have EO/LA ratios ranging from about 0.5 to about 5.0, more preferably about 2.0 to about 4.5, even more preferably about 2.5 to about 3.5 and most preferably about 3.0.

The term "non-crosslinked" or "substantially non-crosslinked" is used to describe polymers which exhibit or display a substantial absence of crosslinking. Polymers according to the present invention which are substantially non-crosslinked are associated with substantial post-surgical adhesion prevention or reduction. In certain embodiments, the

5   present polymers actually prevent adhesions. Polymers according to the present invention which preferably contain less than about 1.0% crosslinking, more preferably less than about 0.5% by weight crosslinking, even more preferably less than about 0.1% by weight crosslinking, most preferably less than about 0.05% by weight crosslinking are advantageously employed in the present invention. As used herein, reference to 1.0%, 0.5%, 0.1% etc.

10   crosslinking refers to the amount by weight of a crosslinker which may be found in the polymers of the present invention.

The polymeric compositions according to the present invention are chain-extended rather than crosslinked. In the present compositions, chain-extension provides the

15   type of structural integrity and uniformity associated with the exceptional performance of the polymers of the present invention as anti-adhesion barriers. While not being limited by way of theory, it is believed that chain-extension, in contrast to crosslinking, allows a degree of mobility and flexibility of the hydrophilic B block which is consistent with anti-adhesion activity. The polymeric compositions according to the present invention provide an

20   environment in which the A blocks (of the ABA triblock) will form stable, hydrophobic hard, and often partially crystalline, microphases of high structural integrity and the B blocks will form hydrophilic, flexible phases, which are believed to be primarily responsible for good anti-adhesion activity. The formation of this microstructure, which is associated with polymeric

compositions according to this invention and in particular, the flexibility of the PEG B blocks, produces excellent barriers for the reduction or prevention of post-surgical adhesions. Crosslinking not only limits molecular mobility, of special importance being its effect on the PEG segments, but also hampers or even prevents microphase segregation from taking place.

5   These two phenomena are seen as being associated with the production of less successful anti-adhesion barriers.

As used in the present invention, the ABA triblocks in the present polymers are chain extended. The chain extenders which are used are difunctional compounds which react

10   with the end-cap group of the triblocks to produce the chain extended triblocks according to the present invention. In the present invention, the amount of chain extender which is included within the polymers according to the present invention may vary. Thus, the molar ratio of chain extender to ABA triblock in the present polymers varies from about 0.5 to about 2.0 (about 1:2 to about 2:1, based upon the number of moles of difunctional chain extender and

15   the number of moles of ABA triblock), more preferably about 0.8 to about 1.2 and most preferably about 1.0. It is noted that in synthesizing the present chain-extended polymers, the amount of chain extender which is reacted with difunctional triblock to produce polymer is generally slightly higher than the amount which is expected to be included in the final synthesized polymers.

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Chain extenders which are used in the present invention, preferably contain no more than about 1% by weight of a crosslinking compound (such term signifying a compound containing at least 3 functional groups which can react with the end-cap group of the triblock

and which generally appear in a chain extender sample as a side product of the synthesis or

production of the chain extender), more preferably, less than about 0.5% by weight of a

trifunctional compound and even more preferably less than 0.1% by weight. It is most

preferable to employ a difunctional chain extender which contains as little trifunctional (or

5   higher functionality) compound as is practical. Also, the occurrence of side reactions which

would lead to crosslinking of the polymers is negligible, due to both compositional as well as

experimental parameters of the synthesis of the polymers of the present invention.

In the case of polymers which are used in structures such as films, the chain

10   extenders are preferably non-water soluble. In the case of polymers which are used in systems

such as water soluble gels, dispersions or viscous solutions, the chain-extenders are preferably

highly water soluble. Preferred water soluble chain-extenders include, for example,

polyethylene glycol diisocyanates, with the polyethylene glycol chain ranging in molecular

weight from about 200 to about 10,000 or more with a preferred molecular weight ranging

15   from about 600 to about 6,000, even more preferably about 600 to about 2,000. In cases

where the preferred embodiment is a non-water soluble polymer in a liquid form, the chain

extenders may also be substantially non-water soluble. The role of the chain-extenders in the

gels and/or viscous solutions according to the present invention is to promote the water

solubility/dispersibility of the polymers in an effort to provide polymers which are readily

20   deliverable to a site in a patient's body.

By utilizing chain extenders rather than crosslinking agents, the present

polymers are substantially non-crosslinked, yet integral, and have the advantage of having

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excellent structural integrity and characteristics such as strength and flexibility, which are advantageous for producing an efficient barrier for preventing adhesions. Also its is believed that the present polymers substantially avoid the formation of particles or break-down products which occur in many of the prior art polymer compositions.

As an advantageous feature of the present invention, substantially non-crosslinked polymers of the present invention are employed in the present invention to substantially reduce or prevent adhesions. While not being limited by way of theory, it is believed that the non-crosslinked polymers according to the present invention allow greater mobility of polyoxyalkylene blocks (and in particular, polyoxyethylene blocks) within the ABA triblock used in the present invention, a condition which is believed to at least partially explain the favorable results obtained by the present polymers in substantially reducing or preventing adhesions. Non-crosslinked polymers according to the present invention are more likely to enhance phase separation of the distinct A and B blocks which comprise the triblocks, a condition which is associated with the superior performance of the polymers of this invention as anti-adhesion barriers.

The term "integral" is used to describe polymers according to the present invention which are substantially non-permeable to mesenchymal cells, platelets, blood cells and other cells which are involved in the biology of adhesion formation. Integral polymers preclude cells which are involved in the adhesion process from crossing the polymer barrier and initiating the adhesion process. Integral polymers also exhibit favorable physical characteristics and mechanical properties consistent with substantially reducing or eliminating

adhesions.

The term "chain-extended" is used to describe polymers according to the present invention wherein the basic triblock is reacted with a difunctional chain-extender to increase the molecular weight of the present polymers. The present polymers are substantially non-crosslinked and are instead, chain-extended to provide sufficiently high molecular weight polymer chains to enhance the strength and integrity of the final polymer compositions as well as affecting the rate of degradation. It is noted that chain extension of the polymers provides adequate stength and integrity of the final films and other structures, yet allows a degree of motility of the individual polyoxyalkylene B blocks within the ABA triblock in order to maximize the adhesion inhibiting characteristics of the films. In contrast, crosslinked polymers provide a more rigid structure which is believed to severely limit movement of the individual polymeric blocks.

The term "biodegradable" relates to the characteristic whereby a polymer will degrade in the body. The polymers according to the present invention readily degrade in vivo and breakdown readily into monomeric units of hydroxy acids. In the case of the PEG chains (B blocks), although these are not biodegradable, they are readily excreted by the patient upon degradation of the A block. The degradation of the present polymers mainly takes place through the hydrolysis of the ester bond in the A block. The hydrolysis reaction is generally dependent upon pH. The rate constant for hydrolysis tends to be much higher at high pH (greater than 9.0) and low pH (less than 3.0) than at neutral pH (6.0 to 8.0). The rate constant for hydrolysis tends to be higher under basic conditions than under acidic conditions.

The polyester A blocks of the triblocks of the present polymers tend to be biodegradable, whereas the poly(oxyalkylene) B blocks of the triblocks and chain extenders tend not to be biodegradable. In the case of water-soluble chain-extenders which are preferably utilized in gels and viscous solutions according to the present invention, these

5   chain-extenders, which generally are highly water soluble, tend not to be biodegradable. In addition, when using polymers containing A blocks derived from α-hydroxy acids, especially from glycolic acid and L-lactic acid, the polymeric A blocks will degrade to individual α-hydroxy acids which are biosynthetically useful and may be involved in the patient's "biochemistry". In contrast, however, although the poly(oxyalkylene) polymeric B blocks are

10   biocompatible, they are neither biodegradable nor bioabsorbable. Thus, in using the polymers according to the present invention it is recognized that the poly(oxyalkylene) blocks will remain as polymeric units in vivo until such time as the blocks are excreted. Consequently, the choice of an upper molecular weight range of the polyoxyalkylene block in the polymers according to the present invention will very much depend on the ability of the body to excrete

15   or otherwise rid the body of the material.

The term " strength", "mechanical strength" or "sufficient suture-holding ablity" describes favorable mechanical and/or physical characteristics of the present polymers and reflects the fact that preferred polymers for use in the present invention (generally, as

20   films) having a mechanical strength which is sufficient to allow a suture to be used to anchor the polymer to a tissue site without appreciable tearing or ripping of the film. These preferred polymers according to the present invention have an Ultimate Tensile Strength value preferably within the range of about 5-35 MPa and Elongation at Break values generally

within the range of about 400-2000%.

The term "flexible" is used with respect to a physical description of the polymers of the present invention to reflect the fact that the present polymers are essentially non-rigid and non-brittle, and generally display an elastomeric behavior and tend to be conformable to a tissue surface to be treated. That is, the present polymers contain sufficient flexibility and are pliable enough to substantially conform to the contours of the tissue surfaces to be treated. Thus, polymeric compositions according to the present invention have a Young's Modulus preferably within the range of about 50-150 MPa.

The term "homogeneous" is used to describe preferred polymers according to the present invention. The term homogeneous is associated with the inclusion in the final polymer compositions of a population of triblocks which are generally of the same size and preferably have a polydispersity of between about 1.0 and 2.0, more preferably about 1.1 to about 1.5 and even more preferably about 1.1 to about 1.2. Homogeneous triblocks are associated with reproducible mechanical and physical characteristics and favorably consistent biodegradability.

The term "structure" is used to describe polymers according to the present invention which have form, size and dimensions which are established outside the body and will not significantly change upon being placed inside the body of the patient to be treated. The term structure embraces not only flat surfaced structures (i.e., films) in the traditional manner, but also cylinders, tubes and other three dimensional structures which are not

substantially changed by the anatomy of the patient into which the structure has been placed.

The term "gels" is used to describe dispersions or suspensions of polymer which have been formed by dissolving, suspending or dispersing polymer in an aqueous

5 solution for delivery to a site within the patient's body in order to prevent adhesions. Gels of the present invention typically contain polymer in a sterile aqueous solution (such solution comprising saline solution, sterile water or a water/ethanol mixture) at a viscosity ranging from about 100 to about 50,000, preferably about 500 centipoise units up to about 20,000 centipoise units or more. More preferably, the gels are delivered in sterile, isotonic saline

10 solution at a viscosity ranging from about 2000 centipoise units up to about 20,000 centipoise units depending upon the application. In certain aspects according to the present invention, liquid polymeric compositions comprising non-water soluble polymers may also be used.

Gels according to the present invention may be used in numerous applications

15 to reduce or prevent adhesions, but preferably are employed to reduce or prevent adhesions following general surgical procedures and related surgeries which are minimally invasive. Gels utilize non-water soluble ABA triblocks which are chain-extended with water-soluble or hydrophilic chain extenders in order to render the overall polymeric composition water dispersible or water soluble. Certain phases within the gel polymer compositions will be

20 advantageously non-water soluble in order to promote the structural integrity and reduce the overall rate of biodegradability of the gel formulations in the body.

The term "viscous solution or suspension" is used to describe solutions or

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suspensions of polymers according to the present invention wherein the solution has a viscosity which is greater than about 1 centipoise unit and is less than about 10,000 centipoise units, more preferably about 10 centipoise units to about 2,000 centipoise units, even more preferably about 100 centipoise units and above within this range. Viscous solutions or suspensions of polymers according to the present invention at viscosities approaching the high end of the range of viscosities may be indistinguishable from gels at the low end of a viscosity range. The present invention also contemplates liquid polymeric compositions having appropriate viscosity and flow characteristics and their use to reduce and/or prevent adhesions.

In the present invention, the ABA triblock is a unit which is generally derived from poly(hydroxy acid) polymers in the A block and poly(oxyalkyelene) polymers in the B block. The A block of the ABA triblocks of the present polymers is biodegradable and ranges in size from one monomeric unit up to about 200 or more monomeric units, with a preferred size ranging from about 4 to about 50 units, more preferably about 6 to about 30 units, even more preferably about 8 to 16 units. The A block preferably is derived from an alpha-hydroxy acid or a related ester or lactone which produces monomer units of alpha-hydroxy acid within the polymeric chain as will be described in greater detail below. More preferably the A block is derived from units of glycolic acid, lactic acid (preferably L, or D,L mixtures to promote bioabsorbability) or mixtures thereof, in the form of glycolide or lactide reactants (dimeric α hydroxy acids as explained in greater detail hereinbelow). The B block preferably comprises poly(ethylene oxide) or poly(ethylene oxide)-co-poly(propyleneoxide) block copolymers. The B block may vary in size from about 200 Da (dalton units) up to about 200,000 Da or higher,

with a preferred range of about 1,000 Da up to about 20,000 Da. Most preferably, the B

block is a poly(ethylene oxide) ranging in size from about 3,000 to about 10,000 Da. It is

unexpectedly that the poly(ethyleneoxide) B block provides the greatest inhibition or reduction
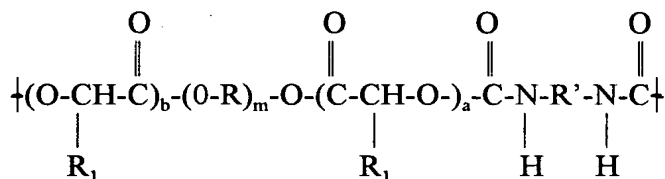
in adhesion in the present invention.

5

The ABA triblock is preferably end-capped with nucleophilic moieties such as

hydroxyl or amine groups. With the preferred nucleophilic end-capping groups in place, the

ABA triblock may be readily chain-extended using difunctional electrophilic compounds such

as diisocyanate or dicarboxylic acid compounds (or derivatives of dicarboxylic acids such as

10   esters or diacyl halides). More preferably, the triblocks are end-capped with hydroxyl groups

and chain-extended with diisocyanate compounds in order to produce the preferred polymers

according to the present invention.

The present invention therefore, relates to a method of substantially reducing or

15   preventing tissue adhesions in patients comprising exposing damaged tissue in a patient to a

polymeric composition in a structure such as a film, gel, dispersion, liquid polymer, spray or

viscous solution form comprising a substantially non-crosslinked, chain-extended multiblock

polymer which preferably is substantially non-water soluble, chain-extended, substantially non-

crosslinked, integral and biodegradable. Structures such as films which incorporate the

20   polymers according to the present invention also are characterized by their favorable

flexibility, mechanical strength and suture-holding ability. Preferably, the molecular weight of

triblocks and polymers used in the present invention are relatively homogeneous which

provides for advantageous characteristics in films and related structures, gels, dispersions,

sprays, liquid polymers and solutions/emulsions.

Preferred polymers used in the present invention as films are poly(α-hydroxy-carboxylic acid)/poly(oxyalkylene) polymers of the chemical structure:

$$\left.\begin{array}{c} O \\ \| \end{array}\right.\quad \begin{array}{c} O \\ \| \end{array}\quad \begin{array}{c} O \\ \| \end{array}\quad \begin{array}{c} O \\ \| \end{array}$$

$$+(O-CH-C)_b-(0-R)_m-O-(C-CH-O-)_a-C-N-R'-N-C+$$

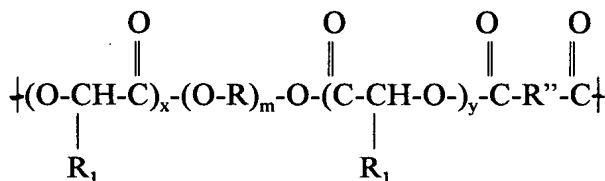$$\begin{array}{cccc} | & & | & | \quad | \\ R_1 & & R_1 & H \quad H \end{array}$$

where a, b and m are positive integers, R is an ethylene and/or propylene group with the proviso that R is not exclusively a propylene group when m is greater than 1, R' is a C_2 to C_{12}, preferably a C_2 to C_8 alkylene group, a cycloalkyl or cycloalkyl-containing group, an aryl or aryl-containing group, 4,4'-diphenylmethane, toluene, naphthalene, 4,4'-dicyclohexylmethane, cyclohexyl, 3,3'-dimethylphenyl, 3,3'-dimethyl-diphenylmethane, 4,6'-xylylene, 3,5,5-trimethylcyclohexyl, 2,2,4-trimethylhexamethylene or p-phenylene and R_1 is H or CH_3. More preferably R' is a hexamethylene group (C_6 alkylene group), R is an ethylene group and R_1 is CH_3. In preferred embodiments, the integers a and b are equal.

Additional preferred polymers for use in the present invention as films include those of the following structure:

$$\begin{array}{cccc} O & O & O & O \\ \| & \| & \| & \| \end{array}$$

$$+(O-CH-C)_x-(O-R)_m-O-(C-CH-O-)_y-C-R''-C+$$

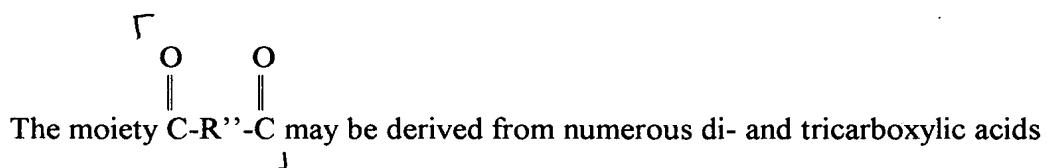$$\begin{array}{cccc} | & & | & \\ R_1 & & R_1 & \end{array}$$

where x, y and m are positive integers, R is an ethylene and/or propylene group with the proviso that R is not exclusively a propylene group when m is greater than 1, R_1 is a hydrogen
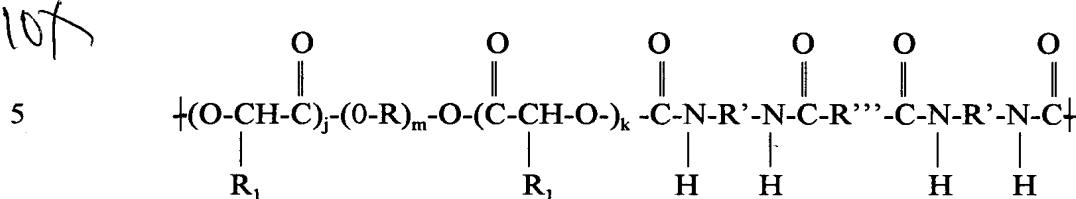
or methyl group, R" is a C_0 to C_{12}, preferably a C_2 to C_8, alkylene group or a hydroxyl or

carboxylic acid substituted alkylene group, alkene, a cycloalkyl, hydroxyl or carboxylic acid

containing cycloalkyl or cycloalkyl-containing group, an aryl or aryl-containing group or a

polyoxyalkylene chain comprised of poly(ethylene oxide), poly(ethylene oxide)-co-

poly(propylene oxide) or other poly(ethylene oxide) rich chains. More preferably, R" is a C_2

to C_4 alkylene group, R is an ethylene group and R_1 is CH_3. The integers x and y are

preferably equal.

$$\left[\overset{O}{\underset{\|}{C}} - R'' - \overset{O}{\underset{\|}{C}} \right]$$

The moiety C-R''-C may be derived from numerous di- and tricarboxylic acids

including, for example, citric acid, malic acid and tartaric acid, among numerous others such as

oxalic acid, malonic acid, succinic acid, 2,3-dimethylsuccinic acid, glutaric acid, 3,3-

dimethylglutaric acid, 3,3-dimethylglutaric aicd, 3-methyladipic acid, adipic acid, pimelic acid,

suberic acid, azelaic acid, sebacic acid, 1,9-nonanedicarboxylic acid,, 1,10-decanedicarboxylic

acid, 1,11-undecanedicarboxylic acid, 1,12-dodecanedicarboxylic acid, maleic acid, fumaric

acid, diglycolic acid, hydromuconic acid, among others, including equivalents of these acids.

These di- and tricarboxylic acids may be used to chain extend the ABA triblocks under

controlled conditions so that crosslinking is substantially prevented. In the case of using

dicarboxylic acids containing additional carboxylic acid groups and/or other polar groups such

as hydroxyl groups, as in the case of citric acid or malic acid, among others, these will tend to

enhance the water solubility of the final polymeric compositions.

Other embodiments according to the present invention relate to polymeric

compositions which have the following general structure:

5

$$\left[(O-CH-C)_j-(O-R)_m-O-(C-CH-O-)_k -C-N-R'-N-C-R'''-C-N-R'-N-C \right]$$

with the carbonyl oxygens (O‖) above the respective carbons, and substituents R_1, R_1, H, H, H, H below.

10   where j, k and m are positive integers, R is an ethylene and/or propylene group with the

proviso that R is not exclusively a propylene group when m is greater than 1, R' is a C_2 to C_{12},

preferably a C_2 to C_8 alkylene group, a cycloalkyl or cycloalkyl-containing group, an aryl or

aryl-containing group, 4,4'-diphenylmethane, toluene, naphthalene, 4,4'-dicyclohexylmethane,

cyclohexyl, 3,3'-dimethylphenyl, 3,3'-dimethyl-diphenylmethane, 4,6'-xylylene, 3,5,5-

15   trimethylcyclohexyl, 2,2,4-trimethylhexamethylene or p-phenylene, R''' is a polyoxyalkylene

chain comprised of poly(ethylene oxide), poly(ethylene oxide)-co-poly(propylene oxide) or

other poly(ethylene oxide) rich chains and R_1 is H or CH_3.   More preferably, R' is a

hexamethylene group (C_6 alkylene group), R is an ethylene group, R''' is poly(ethylene oxide)

and R_1 is CH_3. The integers j and k are preferably equal.

20

        Thus, in various non-preformed materials such as in viscous solutions,

suspensions and gels, the polymers preferably comprise substantially non-water soluble ABA

triblocks as disclosed hereinabove, the chain extension of which is accomplished by using a

highly water soluble/water dispersible chain extender. Although the B block of the ABA

25   triblock is hydrophilic and will have a high degree of compatability with water, thus allowing

certain of the polymeric films according to the present invention to absorb large quantities of

water, it is the hydrophilic chain extender used in various non-preformed polymers such as

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viscous solutions and gels, which allows delivery of these polymer compositions in aqueous

solutions.

In the present application, the following chain extenders find use in preparing

5   non-preformed polymers such as gels and viscous solutions having desirable characteristics for

reducing or preventing post-operative adhesion. It is noted that in choosing ABA triblocks for

formulating viscous solutions and gels according to the present invention, care must be given

to providing a good balance of strength/structural integrity and biodegradability from the A

block, hydrophilicity/anti-adhesion activity from the B block and further hydrophilicity in the

10   form of water solubility/water dispersibility from the chain extender. Thus, non-water soluble

triblocks such as are utilized in film applications according to the present invention are also

advantageously employed in viscous solution/gel applications.

The above chemical formulas provide insight into the chain-extended polymers

15   which are used in the present invention. In the case of polymers which are preferably used in

non-preformed polymers such as gels and/or viscous solutions according to the present

invention, the ultimate polymeric composition is water soluble/dispersible (as opposed to

substantially non-water soluble in the case of polymer structures such as films according to the

present invention) and the polymers are chain-extended utilizing hydrophilic chain extenders,

20   for example, diisocyanate terminated polyalkylene glycol chains comprising a central

polyalkylene glycol chain such as poly(ethylene oxide), capped by two diisocyanate

compounds, among numerous others. Examples include the use of poly(ethylene glycol)

chains with a molecular range between 200 and 20,000, hexamethylene diisocyanate being the

diisocyanate. By employing non-water soluble ABA triblocks and water soluble/dispersible chain extenders, polymer compositions which are used in viscous solution and gel applications provide favorable strength and structural integrity, biodegradability (the rate of which may be influenced by the length and hydrophobicity of the A block and the overall hydrophilicity of

5   the polymer), flexibility and anti-adhesion activity from the PEG segments in the polymer and water solubility/dispersibility from the selective chain extenders which are used.

In addition to being useful for substantially reducing or preventing adhesions, the present polymers may also be used to deliver bioactive compositions to a site of activity

10   within the patient's body. This aspect of the present invention is secondary to the anti-adhesion characteristics of the inventive polymers. It is particularly advantageous that the present polymers may be used to deliver bioactive agents which may serve to enhance the healing of the wounds created by a surgical procedure, a disease state or other condition associated with the tissue to be treated.

15

Exemplary bioactive agents which may be delivered pursuant to the methods according to the present invention include, for example, anticoagulants, for example heparin and chondroitin sulphate, fibrinolytics such as tPA, plasmin, streptokinase, urokinase and elastase, steroidal and non-steroidal anti-inflammatory agents such as hydrocortisone,

20   dexamethasone, prednisolone, methylprednisolone, promethazine, aspirin, ibuprofen, indomethacin, ketoralac, meclofenamate, tolmetin, calcium channel blockers such as diltiazem, nifedipine, verapamil, antioxidants such as ascorbic acid, carotenes and alpha-tocopherol, allopurinol, trimetazidine, antibiotics, especially noxythiolin and other antibiotics to prevent

infection, prokinetic agents to promote bowel motility, agents to prevent collagen crosslinking such as cis-hydroxyproline and D-penicillamine, and agents which prevent mast cell degranulation such as disodium chromolglycate, among numerous others.

5   In addition to the above agents, which generally exhibit favorable pharmacological activity related to promoting wound healing, reducing infection or otherwise reducing the likelihood that an adhesion will occur, other bioactive agents may be delivered by the polymers of the present invention include, for example, amino acids, peptides, proteins, including enzymes, carbohydrates, antibiotics (treat a specific microbial infection), anti-cancer

10   agents, neurotransmitters, hormones, immunological agents including antibodies, nucleic acids including antisense agents, fertility drugs, psychoactive drugs and local anesthetics, among numerous additional agents.

          The delivery of these agents will depend upon the pharmacological activity of the agent, the site of activity within the body and the physicochemical characteristics of the

15   agent to be delivered , the therapeutic index of the agent, among other factors. One of ordinary skill in the art will be able to readily adjust the physicochemical characteristics of the present polymers and the hydrophobicity/hydrophilicity of the agent to be delivered in order to produce the intended effect. In this aspect of the invention, bioactive agents are administered

20   in concentrations or amounts which are effective to produce an intended result. It is noted that the chemistry of polymeric composition according to the present invention can be modified to accommodate a broad range of hydrophilic and hydrophobic bioactive agents and their delivery to sites in the patient.

Synthesis of Polymers According to the Present Invention

In general, the synthesis of the present polymers proceeds by first synthesizing

5   an ABA triblock. In this general reaction, a pre-prepared poly(oxyalkylene) B block (which

can be purchased or synthesized from an initiating diol and an excess of an appropriate

epoxide depending upon the length of the block desired) is reacted with a hydroxyacid or its

cyclic dimer to produce the low molecular weight ABA triblock. Essentially, the

poly(oxyalkylene) block which is generally endcapped with hydroxyl groups reacts with the

10   hydroxyacid or its cyclic dimer to produce ABA triblock which is end-capped with hydroxyl

groups.

Once the ABA triblock is formed, the hydroxyl groups at each end are reacted

with difunctional chain extenders, for example, diisocyanates. This reaction produces a chain

15   extended polymer which is readily used to prepare films and various related structures, gels,

dispersions, suspensions, and viscous solutions of the present invention. In the case of liquid

polymers, these are of sufficiently low molecular weight so that they are in liquid form without

the need to add additional solvent.

20   Generally, during the first stage of the reaction in which the low molecular

weight ABA triblock is formed, the overall molecular weight and the length of the different

segments will be determined by the molecular weight of the poly(oxyalkylene) block chosen to

initiate the reaction, by the number of moles of hydroxyacid or its cyclic dimer, which is

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reacted with the poly(oxyalkylene) block and the catalyst and various experimental parameters such as the heat and the reaction time. Thereafter, the ABA triblock is chain-extended to produce polymers containing ABA triblocks.

5   A preferred synthesis of the present polymers involves the use of the cyclic ester or lactone of lactic acid and glycolic acid. The use of lactide or glycolide as the reactant will enhance the production of which will produce the ABA triblocks.

          In this preferred method, lactide or glycolide (the cyclic dimer of lactic acid or 10 glycolic acid, respectively), rather than lactic acid or glycolic acid, is first used to synthesize the ABA triblock from the starting poly(oxyalkylene) block. Once the ABA triblock is obtained, the hydroxyl end-capped ABA triblock is reacted with a diisocyanate, preferably hexamethylene diisocyanate.

15   The synthesis of the ABA triblock proceeds by way of a ring-opening mechanism, whereby the ring opening of the lactide or glycolide is initiated by the hydroxyl end groups of the PEG chain under the influence of a tin catalyst (stannous octoate). An ABA type triblock is generated at this point, the molecular weight of which is a function of both the molecular weight of the central PEG chain and the length of the PLA lateral blocks. Typically, 20 the molecular weight of the triblock spans between about 4,000 to about 30,000 (but may be as low as 1,000 or less and as high as 250,000 or more). After synthesis of the ABA triblock, the final polymer is obtained by chain extending the hydroxyl terminated triblocks with difunctional reactants such as isocyanates, most preferably hexamethylene diisocyanate.

The chemical and physical properties of the different polymers will vary as a function of different parameters, the molecular weight of the PEG and PLA segments along the backbone being of particular importance.

The preferred method has several advantageous characteristics including:

1. a rapid, nearly quantitative reaction which is complete in from 1 to 3 hours;

2. the reaction takes place under moderate reaction conditions (140°C) thus minimizing side reactions;

3. the resulting triblock contains an extremely narrow polydispersity (P= 1.3-1.4 or better; and

4. the triblock contains little or no homopolymer.

Preparation of Adhesion Barrier Structures

Barrier structures (which term includes films as well as cylinders and related three-dimensional structures) for use in the present invention are prepared by first producing the polymer according to the present invention and then dissolving the polymer in a solvent, such as chloroform, methylene chloride or a related organic solvent. Films, for example, are preferably prepared by placing the solution containing polymer in a mold or a related receptable and then allowing the solvent to evaporate. The resulting film is homogeneous and of uniform thickness and density. The film may be used as prepared or cut into segments for application to a desired site in a patient. In addition to the above-described solvent cast method, a continuous solvent cast process, a thermal cast method or related methods well

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known in the art may be used to make films and other structures according to the present invention.

In order to prepare other three dimensional structures of polymer, such as cylinders and related shapes, these may be cast or molded using various techniques, starting with solid polymer. Methods to produce these structures using these techniques are well known in the art.

Preparation of Gels, Viscous Solutions and Dispersions

In order to prepare the gels, viscous solutions and dispersions according to the present invention, polymer in powder, flakes or other related form is dissolved or suspended in an aqueous solution, preferably sterile isotonic saline solution, generally at room temperature and then mixed in the solution to produce the final gel, viscous solution or dispersion. Viscosity of the system is readily adjusted by adding further polymer or aqueous solution. The gels, viscous solutions and dispersions are utilized under sterile conditions.

While not being limited by way of theory, it is believed that the chain extended polymers of the present invention form integral layers in films, gels or viscous solutions when applied to tissue for surgical applications. The resulting integral polymers provide an excellent barrier which substantially reduces the formation of post-operative adhesions.

Having generally described the invention, reference is now made to the following examples intended to illustrate preferred embodiments and comparisons but which are not to be construed as limiting to the scope of this invention as more broadly set forth above and in the appended claims.

5

EXAMPLES

Example 1

Effect of Polymer Films on Adhesion

The purpose of this experiment was to test the efficacy of EO/LA films (ratios

10   2.5, 3.3. and 4.0) on the formation of adhesions in a rabbit model of adhesion formation between the sidewall and the bowel.

Materials and methods

15   Animals

Twenty female New Zealand rabbits, 2.4-2.7 kg, were purchased and quarantined for at least 2 days prior to use. The rabbits were housed on a 12:12 light: dark cycle with food and water available ad libitum.

20   Synthesis of Materials

The synthesis of the polymers can be summarized as follows:

1. ABA triblock was synthesized as follows:

Polyethylene glycol (MW=6,000) was dried in vacuo overnight at 80°C. Thereafter,

the PEG was cooled down to room temperature, the vacuum was broken by flushing dry N_2

through the system and lactide is thereafter added in an appropriate amount (depending upon

the length of the A block desired). The mixture of PEG and lactide is placed in an oil bath at

140°C and after 2-3 minutes (which is generally required to homogenize the system), stannous

5   octoate is added (the catalyst/lactide mole ratio is 1/400). The mixture is then flushed with N_2

for a period of about 5 minutes, whereupon the N_2 is removed and the flask containing PEG

and lactide is then capped and stirred at 140°C in an oil bath for 2 hours. At the end of a 2

hour period, the mixture is removed from the oil bath, allowed to cool, dissolved in

chloroform and precipitated in ether. The precipitate is thereafter collected and dried

10   overnight in vacuo at 50°C. It is then solubilized in chloroform and the chloroform is

evaporated to form a film of approximately 10 mil thickness.

2. The Polymer was synthesized as follows:

The synthesis of the polymers is completed by chain extending the ABA triblocks by

15   reacting their hydroxyl-terminated groups with diisocyanates, typically hexamethylene

diisocyanate (HDI). The triblock obtained above is dried at 80°C in vacuo for a period of two

hours. After the two hour period, vacuum is broken by flushing N_2 through the system and a

minimal amount of dry dioxane to dissolve the triblock is added. The required amount of

catalyst is dissolved in dioxane (about 5 ml) and added to the triblock. 15 ml of dry dioxane is

20   introduced into a separatory funnel and the required amount of HDI is added (the HDI:catalyst

molar ratio is 5:1, and the HDI is in a 7% molar excess respective to the triblock- the typical

Triblock:HDI:Catalyst molar ratios are, therefore, 1.0:1.07:0.2, respectively). Once the

triblock is fully dissolved, the HDI solution is added dropwise (over a period of 30 minutes) to

the triblock solution. A condensor is then connected to the reaction flask to prevent dioxane

loss and the reaction is continued for a period of 2.5 hours. After 2.5 hours, the reaction is

removed from the oil bath, allowed to cool and the polymer solution is precipitated with ether.

The precipitated polymer is then collected and dried overnight at 50°C. The material is then

5   solubilized in chloroform and the chloroform is evaporated (room temperature overnight

followed by 5 hours under vacuum at 40°C) to form a film of approximately 10 mil thickness.

The final polymers used in this experiment had EO/LA ratios of 2.5, 3.3 and

4.0.

10   Materials: The above-obtained films were used in the following experiments. The sutures

used were as follows: 6-0 Prolene (Ethicon, Raritan, NJ) was used to tack the film in place

and 3-0 coated Dexon II suture (Davis and Geck, Manati, PR) was used to close the

peritoneum and skin.

15   Sidewall Model: Rabbits were anesthetized with a mixture of 55 mg/kg ketamine

hydrochloride and 5 mg/kg Rompun intramuscularly. Following preparation for sterile

surgery, a midline laparotomy was performed. The cecum and bowel were exteriorized and

digital pressure was exerted to create subserosal hemorrhages over all surfaces. The damaged

intestine was then lightly abraded with 4" 4 x 4 ply sterile gauze until punctate bleeding was

20   observed. The cecum and bowel was then returned to its normal anatomic position. A 3 x 3

cm^2 area of peritoneum and transversus abdominous muscle was removed on the right lateral

abdominal wall. The prepared film (see below) was sutured in place using 6-0 prolene at 6

sites (at each corner and in the center of the side of the film on two sides). After 31-32 days,

the rabbits were terminated and the percentage of the area of the sidewall injury that was involved in adhesions was determined. In addition, the tenacity of the adhesions was scored using the following system:

5
        0 = No adhesions

        1 = mild, easily dissectable adhesions

        2 = moderate adhesions, non-dissectable, does not tear the organ

        3 = dense adhesions, non-dissectable, tears organ when removed

10   A reduction in either the area or the tenacity of the adhesions was considered to be beneficial.

Preparation of Film: The films were stored at room temperature in a desiccator until the day of surgery. On the day of surgery, the film was cut to 3 cm x 3 cm in sterile conditions. Ten to 12 minutes prior to placement, the film was placed in sterile, double distilled water to allow

15   hydration. During hydration, the films went from opaque to clear and increased in size proportionate to the EO/LA ratio (the higher the ratio the more the increase). Thereafter, the film was rinsed with phosphate buffered saline (pH 7.4) to restore isotonicity to the surface. Just prior to placement, the film was blotted on sterile gauze to remove excess moisture.

20   RESULTS: During the early postoperative interval, two rabbits died. Coincidentally, both received the film of the 3.3 ratio. Postmortem necropsy revealed nothing unusual and the deaths were attributed to the surgical procedure. No inflammation was noted intraperitoneally.

One rabbit from the group that received the film with the ratio 2.5 was sacrificed 13 days later. Some material was present at the site (identity unknown). One rabbit from the group that received the film with the ratio 4.0 died 24 days after surgery. No reason for the mortality was noted upon necropsy.

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One month after surgery, the remaining rabbits were sacrificed and the degree of adhesion formation determined (Table 1). At surgery, 5 rabbits were controls. However, at necropsy, 6 rabbits had been given control numbers with two rabbits given the same number (1-2 on the surgery day). One number from the group that had film with the ratio 4.0 was missing (2-1 from surgery day). Of the rabbits that were confirmed as controls (4 of the 6), 3 had adhesions (one with 80% and 2 with 100% of the area of the sidewall injury with adhesions). In all of these rabbits, the tenacity of the adhesions was 3+. All of the rabbits with films placed at surgery had no adhesions at necropsy. Of the two rabbits with the same number, one had 100% of the sidewall injury area covered with 3+ adhesions and the other had no adhesions at the site of injury.

DISCUSSION: The films made from various ratios of EO/LA were highly efficacious at the reduction of adhesion formation. In the control rabbits which had surgery and the sutures placed in the same pattern as that in the treated rabbits, the majority (60%, 75% or 80% depending upon the inclusion of the mismarked rabbit) of the rabbits had the formation of severe, cohesive adhesions at the site of sidewall injury. In the rabbits that were confirmed to have been given the film,, all rabbits had no adhesions at the site of adhesion formation. At two weeks and later, the site of injury appeared fully healed.

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Table 1. Area of Adhesion Formation at Site of Sidewall Injury

% Area Involved

	Treatment	0	1-25	26-50	51-75	76-100
5	Surgical Control n=4	20*	0	0	0	75
	EO/LA Ratio 2.3 n=4	100	0	0	0	0
10	EO/LA Ratio 3.3 n=3	100	0	0	0	0
	EO/LA Ratio 4.0 n-3	100	0	0	0	0

15   * 1 out of 5 animals had no adhesions.

It is to be understood that the examples and embodiments described hereinabove are for the purposes of providing a description of the present invention by way of example and are not to be viewed as limiting the present invention in any way. Various

20   modifications or changes that may be made to that described hereinabove by those of ordinary skill in the art are also contemplated by the present invention and are to be included within the spirit and purview of this application and the following claims.